REMARKS

Claims 1, 2, 4-15 and 72-83 were pending. Upon entry of this amendment, claims 1, 2, 4-15 and 76-83 will be pending. Claims 1, 11 and 76 are amended herein to limit the region the antisense compounds are targeted to, or specifically hybridize with, to nucleotides 1 through 970 of human hormone-sensitive lipase (SEQ ID NO: 3). Claims 72-75 are cancelled. The claim amendments and cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claim 15 is rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. The Examiner concedes that the specification is enabling for in vitro inhibition of human hormone sensitive lipase of SEQ ID NO: 3 by administration of antisense oligonucleotides that target and specifically inhibit expression of SEQ ID NO: 3. The Examiner further states that the specification is enabling for in vivo targeting and inhibition of SEQ ID NO: 3 in mouse liver to decrease liver weight, decrease serum insulin levels in ob/ob mice, and decrease serum cholesterol and triglycerides in ob/ob mice and a P-407 hyperlipidemia mouse model using the antisense oligonucleotide of SEQ ID NO: 179. The rejection, however, was based on the examiner's assertion that the specification does not enable in vivo inhibition of hormone-sensitive lipase using any antisense for reasons set out in a previous Office Action mailed January 14, 2003.

The Office Action also refers to comments filed by Applicants on July 1, 2004. Applicants assume the Office Action intended to reference Applicants' remarks made in the response after final rejection filed May 24, 2004, which were not entered, but were re-submitted with the Request for Continued Examination filed September 2, 2004. In response to Applicants' comments, the Examiner alleges that administration of SEQ ID NO: 179 is not representative of the ability to target and inhibit hormone-sensitive lipase expression in vivo using any antisense, because the success of one antisense molecule is not predictive of the ability of another antisense molecule to achieve adequate uptake, target binding and

inhibition of target gene expression. Thus, the Office Action concludes, it would require undue experimentation to identify other antisense compounds that inhibit expression of hormone-sensitive lipase in vivo.

Claim 15 is directed to a method of inhibiting expression of hormone-sensitive lipase in cells or tissues comprising contacting the cells or tissues with a compound of the invention at a concentration sufficient to inhibit expression of hormone-sensitive lipase. Applicants respectfully disagree that claim 15 lacks enablement for inhibition of hormone-sensitive lipase in cells or tissues *in vivo*. Based on the teachings of the specification and presence of working examples, Applicants submit that undue experimentation is not required by one of skill in the art to identify additional antisense compounds that would inhibit hormone-sensitive lipase in vivo.

The specification provides numerous working examples demonstrating that antisense oligonucleotides to hormone-sensitive lipase effectively reduce target gene expression in vivo as well as elicit a variety of desired biological responses. For instance, Example 20 demonstrates that in vivo administration of a compound of the invention inhibits liver mRNA expression of hormone-sensitive lipase in a mouse model of obesity and Example 19 shows that administration of the compound reduces blood glucose levels. Furthermore, in the same mouse model of obesity, a compound of the invention is shown to reduce liver weight without affecting fat weight (Example 21), decrease serum insulin levels (Example 22), decrease liver enzyme AST and ALT levels (Example 23), and decrease serum cholesterol and triglyceride levels (Example 24). In additional in vivo studies, compounds of the invention are tested in a mouse model of hyperlipidemia. Examples 28 and 29 demonstrate that an antisense oligonucleotide to hormone-sensitive lipase reduces target mRNA expression in the liver and reduces serum cholesterol and serum triglyceride levels. Therefore, the specification teaches in two distinct animal models of metabolic disease, compounds of the invention can be administered in vivo to inhibit hormone-sensitive lipase gene expression in cells and tissues.

The specification further provides a large number of compounds (see, for example, Table 2 on pages 89-90 of the specification) designed to target human hormone-sensitive

lipase and which inhibit expression of hormone-sensitive lipase in cells. In order to achieve target mRNA inhibition, antisense compounds must necessarily achieve adequate uptake and target binding. Undue experimentation would not be required for one of skill in the art to design or select additional antisense compounds for inhibition of hormone-sensitive lipase in cells or tissues vivo given the teachings of the specification. Because the specification provides a more than adequate teaching of antisense compounds that are amenable to cellular uptake, target binding and inhibition of gene expression, and the specification provides numerous working examples demonstrating in vivo administration and biological effects of hormone-sensitive lipase antisense compounds, Applicants submit that the claimed invention is enabled.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection.

Claims 72-75 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. Without responding to the merits of this rejection, Applicants have cancelled claims 72-75 without prejudice, thus rendering the Examiner's rejections moot. Applicant reserves the right to file subsequent applications claiming the cancelled subject matter. In addition, the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant respectfully requests reconsideration and withdrawal of these grounds for rejection.

REJECTION UNDER 35 U.S.C. §102(a)

Claims 11-14 and 76-80 are rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Mitchell *et al.* (WO 01/26664). The Office Action states that Mitchell *et al.* teach compositions comprising oligonucleotide mimetic compounds between 8-50 nucleobases which specifically target an active site on and inhibit the expression of hormone-sensitive lipase (SEQ ID NO: 3) in vitro; antisense compounds with phosphorothioate linkages and 2'-O-methoxyethyl modified sugars; compositions comprising a pharmaceutically acceptable carrier; and a colloidal dispersion system.

Applicants respectfully traverse the rejection; however, solely in the interest of advancing prosecution, claims 11 and 76 have been amended herein. Claim 11, as amended, is directed to compounds 8 to 50 nucleobases in length which specifically hybridize with at least an 8-nucleobase portion of an active site on nucleotides 1 through 970 of a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3). Claim 76, as amended, is directed to an oligonucleotide mimetic compound 8 to 50 nucleobases in length targeted to nucleobases 1 through 970 of a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3), wherein said compound specifically hybridizes with and inhibits the expression of hormone-sensitive lipase.

For a reference to anticipate a claim, each element recited in the claim must be found either expressly or inherently described in a single prior art reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Mitchell *et al.* fail to teach each and every element of the claimed invention.

As currently amended, claims 11 and 76, and by dependency, claims 12-14 and 77-80, specify that the compound is specifically hybridizable with or targeted to nucleobases 1 through 970 of human hormone-sensitive lipase (SEQ ID NO: 3). Mitchell *et al.* do not teach any compounds that specifically hybridize with at least an 8-nucleobase portion of an active site on nucleotides 1 through 970 of a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3). Mitchell *et al.* also do not teach any oligonucleotide mimetic compounds targeted to nucleobases 1 through 970 of a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3).

Since Mitchell *et al.* do not disclose each limitation of the claims, the reference fails to anticipate Applicant's claimed invention. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102(a).

REJECTIONS UNDER 35 U.S.C. §102/103

Claims 1, 2, 11, 12, 14 and 72-75 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Holly *et al.* (US 5,502,034) and Strosberg *et al.* (WO 96/34100). The Office

Action states that Holly *et al.* and Strosberg *et al.* teach antisense oligonucleotides 8-50 nucleobases in length that specifically hybridize with nucleotides 1143-3775 of a nucleic acid encoding human hormone-sensitive lipase (SEQ ID NO: 3).

Claims 72-75 have been canceled herein, rendering the rejection as applied to these claims moot. Applicants respectfully traverse the rejections in regard to claims 1, 2, 11, 12 and 14; however, solely in the interest of advancing prosecution, Applicants' have amended claims 1 and 11 herein. As amended; claim 1 specifies that the compound specifically hybridizes with nucleotides 1 through 970 of human hormone-sensitive lipase (SEQ ID NO: 3). Similarly, claim 11 is amended to specify that the compound specifically hybridizes with at least an 8-nucleobase portion of an active site on nucleotides 1 through 970 of a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3). Thus, neither Holly *et al.* nor Strosberg *et al.* anticipate or render obvious, claims 1, 2, 11, 12 and 14. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(b), or in the alternative, 35 U.S.C. §103(a).

REJECTION UNDER 35 U.S.C. §103(a)

Claims 1, 2, 4-15 and 72-83 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Mitchell *et al.* and Strosberg *et al.* in view of Langin *et al.* (Proc. Natl. Acad. Sci. U.S.A. 90:4897-4891, 1993) and Holst *et al.* (Genomics 35:441-447, 1996), the combination in view of Milner *et al.* (Nature Biotech. 15:537-541) and McKay *et al.* (US 6,133,246), the combination in view of Laurell *et al.* (Biochem. J. 328:137-143, 1997) and Kosaki *et al.* (J. Biol. Chem. 270:816-820, 1995).

The Office Action states that Holst *et al.* and Langin *et al.* teach antisense oligonucleotides 8-50 nucleotides in length targeting human hormone-sensitive lipase and that these references further teach that hormone-sensitive lipase is a regulator of energy homeostatis (Holst *et al.*) and plays a role in obesity and diabetes (Langin *et al.*), providing a motivation to study this protein. Milner *et al.* is alleged to teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize with and inhibit expression of a target gene of known sequence. McKay *et al.* is alleged to teach compositions comprising antisense oligonucleotides 8-50 nucleotides in length comprising various

modifications, compositions comprising the antisense oligonucleotides and compositions further comprising a colloidal dispersion system and pharmaceutically acceptable carrier. The Office Action further states that Laurell *et al.* teaches the biological roles of hormone-sensitive lipase and Kosaki *et al.* teach the use of HepG2 cells as a model cell line.

The Examiner concludes that it would have been obvious to one of skill in the art to design and utilize antisense oligonucleotides to inhibit expression of hormone-sensitive lipase (SEQ ID NO: 3) in vitro because of the teachings of Milner *et al.* and McKay *et al.*, and that Mitchell *et al.* and Langin *et al.* provide the nucleotide sequence of hormone-sensitive lipase while Strosberg *et al.* teach oligonucleotides that specifically target hormone-sensitive lipase nucleotides 1143-3775. The Examiner further states that the remaining cited references provide motivation for inhibiting hormone-sensitive lipase, using HepG2 cells and incorporating nucleotide modifications.

To establish a *prima facie* case of obviousness, the prior art reference, or references, must teach or suggest all of the claim limitations. As currently amended, each of the claims include the limitation that the compounds target or specifically hybridize with nucleobases 1 through 970. None of the cited references, either singly or in combination, teach or suggest antisense compounds that specifically target nucleobases 1 through 970 of human hormone-sensitive lipase (SEQ ID NO: 3).

Accordingly, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness and request that the rejection under 35 U.S.C. §103(a) be withdrawn.

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If the Examiner is of a contrary view, the Examiner is requested to contact the undersigned attorney at (760) 603-2777. Please charge any deficiencies to Isis Pharmaceuticals, Inc., Deposit Account No. 50-0252, referencing Attorney Docket No. ISPH-0587.

Respectfully submitted,

Date: **May 17, 2005**

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